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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,043	12/09/2005	Michael R Downes	SALK3130-1S	2033

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EXAMINER	
ZAREK, PAUL E	
ART UNIT	**PAPER NUMBER**
4161	
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08/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,043	DOWNES ET AL.	
	Examiner	Art Unit	
	PAUL ZAREK	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,21,25,26,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,21,25,26,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/11/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 15-20, 22, 23, and 27-35 have been canceled by the Applicant. Claim 14, 21, 25, and 26 were amended on in correspondence filed on 05/13/2005. Claims 1-14, 21, 24-26, 36, and 37 are currently pending. This is the first Office Action on the merits of the claim(s).

Priority

2. Applicant's claim for the benefit of a prior-filed provisional application, 60/426,664 (filed on 11/15/2002), and a CIP of application 10/658,115 (filed on 09/08/2003, abandoned on 09/19/2006) under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

3. Acknowledgment is made of applicant's claim for foreign priority to Application No. PCT/US2003/036137 (filed on 06/21/2004) under 35 U.S.C. 119(a)-(d).

Claim Rejections - 35 USC § 112 (1st Paragraph)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4-14, 21, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* screening assay to identify processes regulated by FXR activation and a method of treating hypercholesteremia and

cholestasis, does not reasonably provide enablement for methods of modulating processes *in vivo* comprising administering the claimed compound . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

6. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

a. *The breadth of the claim*: Claims 1-14, 21, and 24-26 of the instant application are drawn to a method of "modulating process(es) mediated by farnesoid X receptor (FXR) polypeptides, said method comprising conducting said process(es) in the presence of an effective amount of at least one compound having the [claimed] structure." Applicant defines "modulating" as the ability of the modulator (i.e. the claimed compounds) to induce or repress the expression of genes under hormone expression control (paragraph 0076). This can reasonably be interpreted to include any protein whose expression is affected in any manner by any gene that is influenced in any manner by the addition of the claimed compound (Claim 1) to any system comprising the farnesoid X receptor, or any variant, either natural or man-made, thereof, at any point in time following addition of the claimed compound;

b. *Nature of the invention*: The nature of the invention is drawn to a method of affecting the regulation of genes associated with FXR or a screening assay in which the output is a variation in gene expression;

c. *The state of the prior art*:

The FXR is an integral part of the cholesterol biosynthesis pathway. The FXR serves as a biosensor of bile acids and is part of a feedback inhibitory loop wherein an elevation of cholesterol metabolism leads to an increase in bile acids, which activate the FXR, which leads to an inhibition of cholesterol metabolism. FXR agonists, such as GW4064 (which is structurally unrelated to the claimed compounds) can also block cholesterol metabolism;

d. *Level of one of ordinary skill in the art*: One of ordinary skill in the art would include scientists and physicians investigating the molecular pathways associated with cholesterol;

e. *Level of predictability in the art*: FXR agonists have been shown to be effective in treating hyperglycemia and hyperlipidemia. However, the FXR plays a central role in a wide variety of intracellular pathways and activation of FXR may lead to opposite effects depending on tissue and cell type. "The finding that . . . FXR is also expressed in nonclassical bile acid target tissues suggests that potentially it has a far greater number of roles throughout the body that originally assumed." (Scotti, et al., Cellular and Molecular Life Sciences, 2007, pg 2487, col 1, paragraph 2, lines 19-23). Moreover, Fiorucci, et al. (TRENDS in Molecular Medicine, 2007), teach that much remains unknown about the effects of FXR modulation: "activation of FXR might have a dark side: There are several possible side effects, the most important of which are the inhibition of conversion of cholesterol into Bas (Bile Acids) and the reduction of HDL levels. . . . Many research questions remain and the full validation of FXR as a major therapeutic

target *can only be obtained* through positive results from ongoing clinical trials." (pg 307, "Conclusions" section, line 8 through pg 308, line 3, emphasis added);

f. *Amount of direction provided by the inventor*: Applicant states that modulating FXR either increases or decreases gene expression under hormone expression control. Applicant does not disclose what the ultimate effects of increasing or decreasing a specific gene listed in the Appendix would be;

g. *Existence of working examples*: Applicant provides EC_{50} values for a large number of species encompassed within the claimed genus (Tables 1-15). Applicant provides a summary, but not complete listing, of genes that are either upregulated or downregulated by addition of Fex to a hepatocyte cell system (Appendices I and II). Many of the genes listed are clone, such as AP000501, "Homo sapiens genomic DNA chromosome 8p11.2, clone:91H23 to 9-41," and their function unknown (pg 60); and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Applicant claims that the present invention would be successful for modulating <u>any</u> process under hormonal control. While Applicant has convincingly demonstrated the efficacy of activating FXR with the genus claimed, the sheer number of "process(es)" that can be affected by such treatment is staggering in scope and may be contradictory in nature (Scotti, et al., pg 2487, col 2, lines 4-10). Disclosure of a representative sample of genes affected by FXR activation, a significant portion of which whose function is unknown, would not enable on of ordinary skill in the art at the time the invention was made to use the invention. Therefore, Claims 1, 4-14, 21, and 24-26 are

enabled only for an *in vitro* screening assay or as a treatment for hypercholesteremia or lipid homeostasis. To use the claimed invention outside of the screening assay or treatment for hypercholesteremia or lipid homeostasis, one of ordinary skill in the art would have to identify a gene or gene product that would be susceptible to FXR modulation, predict how FXR would modulate that gene or gene product, and administer an appropriate amount of the drug sufficient to achieve the desired result. If unsuccessful, which is likely given the complex and differential effects of FXR agonism, one of ordinary skill in the art would have to determine another gene or gene product that could be modulated in a desired fashion. The instant specification does not overcome the deficit of the art to allow a skilled artisan to use the invention. Unpredictable and unguided experimentation would be required to use the invention commensurate with the rejected claims.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-14, 21, and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 1-14, 21, and 24-26 are drawn to "a method for modulating process(es) mediated by farnesoid X receptor polypeptides, said method comprising conducting said process(es) in the presence of an effective amount of at least one compound having the

[claimed] structure." This does not recite the milieu in which the process is performed or what is to be accomplished. Even if it were recited that the compound was used to treat a disease condition moderated by the farnesoid receptor it would be indefinite because the disease state for which it is useful could not be determined. The rejected claims also recite "process(es)." This is indefinite because it is unclear how many processes would be affected, how and to what extent they would be affected, and at what point following treatment with the claimed compound (minutes, hours, days, etc) that the processes would be affected.

10. Claim 12 recites the limitation "R^3 as –CH=CH-C(O)-O-tBu." There is insufficient antecedent basis for this limitation in the claim. R^3, then, is a substituted alkenyl. Claim 12 depends upon Claim 11, which limits R^3 to alkenyl. Applicant defines alkenyl as a "straight or branched chain hydrocarbyl group having at least one carbon-carbon doublebond, and having in the range of about 2 up to 20 carbon atoms, and 'substituted alkenyl' refers to alkenyl groups further bearing one or more substituents as set forth above" (paragraph 0010). By Applicant's definition, R^3 in Claim 12 is a substituted alkenyl, not an alkenyl. Since Claim 12 depends upon Claim 11, which limits R^3 to alkenyl, but not substituted alkenyl, Claim 12 lacks antecedent basis for the limitation of R^3.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not

identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-14, 21, 24-26, 36, and 37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12, 19, and 22-24 of copending Application No. 10/535,041. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '041 application are drawn to FXR modulators that are identical to those used to claimed in the instant application for the treatment of FXR-mediated processes, hypercholesterolemia, or cholestasis. Claim 1 of the '041 application correspond to Claims 1-3, 36 and 37 of the instant application. Claims 2-12, 19, and 22-24 correspond to Claims 4-14, 21, and 24-26 of the instant application, respectively. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) (MPEP § 2112).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL ZAREK whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, PATRICK NOLAN can be reached on (571) 272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4161